Key Concepts

• About two thirds of deaths after the first year following liver transplantation are unrelated to graft function.
• Obesity and components of the metabolic syndrome are important risk factors for many of the most common causes of mortality following liver transplantation.
• The ideal approach to obesity, hypertension, dyslipidemia and diabetes in liver transplant recipients requires consideration of factors unique to the posttransplant recipient, especially management of immunosuppression.
• The frequency of malignancies is greatly increased among liver transplant recipients, who are at risk of a distinct spectrum of neoplasia.
• Liver transplant recipients should undergo specific screening and management protocols to screen and treat features of the metabolic syndrome and neoplasia. The great variability between liver transplant centers in longer outcomes is likely to be contributed to by variation in the approach to these issues.
• Because of the central role of immunosuppression in common causes of morbidity and mortality following liver transplantation, the minimum degree of immunosuppression needed to achieve excellent allograft function should be sought for recipients.

Summary

Longterm survival following liver transplantation is profoundly affected by conditions unrelated to graft function. Many of the causes of mortality in liver transplant recipients, including cardiovascular disease, renal failure and malignancies, are contributed to by the metabolic syndrome. The approach to metabolic syndrome in liver transplant recipients requires consideration of transplant specific factors, particularly immunosuppression. Irrespective of the presence of MS, enhancing longer outcomes for liver transplant recipients necessitates minimizing the amount of immunosuppression required to prevent rejection. Early recognition, prevention and treatment of features of the metabolic syndrome and screening for malignancy are likely to enhance survival following liver transplantation. The great center to center variability in longer outcomes suggests room for improvement in the longer term management of liver transplant recipients. Studies to determine the optimal approach to minimize the impact of metabolic syndrome and complications of immunosuppression in transplant recipients are needed.

Introduction

Although the concept of “Regenerative Medicine” as a respectable and viable field is relatively new, the desire to replace failing organs and tissue is ancient. The first
allotransplantation procedure to be extensively, if not entirely credibly, documented was performed by the 3rd-century saints Damian and Cosmas, who replaced the cancerous leg of the Roman deacon Justinian with the leg of a recently deceased Moor. Most descriptions have the saints performing the transplant in the 4th century, many decades after their deaths, giving rise to a tincture of scepticism with regard to the accuracy of accounts of the procedure and its subsequent success. Historically accurate or not, the leg transplant performed by Damian and Cosmas, who went on to become the patron saints of surgeons, exemplifies the subsequently enduring tradition of the willingness of surgeons to conduct allotransplant procedures well ahead of the development of the knowledge and tools required for patients and organs to survive the procedure. Solid organ transplantation is, in essence, a form of vascular surgery, the pioneering techniques of which were developed in the early 1900s by the French surgeon and subsequent Nobel Laureate Alexis Carrel, whose masterful arterial and venous anastomosis suturing techniques laid the groundwork for transplant surgery performed to this day. The technical hurdles proved, however, to be simpler to solve than immunological barriers, with rejection providing an insurmountable obstacle for decades. Professor Thomas Starzl performed five human liver transplants between March and October of 1963. The longest patient survival was 21 days. Shortly after Starzl’s initial procedures, surgeons in Boston and Paris made single, failed attempts at liver transplantation. In the wake of these poor results, the medical community agreed to a moratorium on liver transplants that lasted for three years.

The evolution of liver transplantation from an experimental procedure to a nearly routine operation, limited only by the number of available donor organs, has been one of the most remarkable achievements in medicine. There are currently over 15,000 liver transplants performed annually in the North America, South America and Europe. The Scientific Registry of Transplant Recipients reports that over 60,000 liver transplant recipients are alive with a functioning graft in the United States alone. Currently, overall 3-year patient survival following liver transplantation in the United States is 80%, with a 10-year survival rate of ~50% (http://www.unos.org). Patient and graft survival rates continue to improve year to year (Figure 1) despite steady increases in the severity of illness (as measured by MELD score) and increasing recipient and donor age at time of transplantation (Figure 2). The sequential improvements in patient and graft survival following liver transplantation have been contributed to by many factors. They have also been inversely related to the frequency of steroid resistant rejection, which now accounts for less than 4% of long-term graft loss (1). Hepatic etiologies, including recurrence of HCV, are the basis of only one third late posttransplant deaths,(2) increasing the importance of non-hepatic causes. The emergence of highly effective calcineurin inhibitor (CNI) based immunosuppression regimens has, thus, come with a cost of toxicities. The current overriding unmet clinical need in liver transplantation has transitioned from improved efficacy of immunosuppression to improved tolerability. Understanding non-graft related causes of longterm mortality is critical to enhancing outcomes. Optimization of outcomes has become increasingly important in the current era of outcomes monitoring and wide dissemination of center-specific performance.
Causes of Death Following Liver Transplantation

The most robust data regarding medium and long-term causes of mortality following liver transplantation were generated by the National Institute of Diabetes and Digestive and Kidney (NIDDK) Diseases prospective multicenter study.(2) Causes of death >1 year were: 28% hepatic, 22% malignancy, 11% cardiovascular, 9% infection, 6% renal failure.(2) Renal-related death increased dramatically over time. Recurrence of hepatitis C is, by far, the most common cause of late hepatic related mortality. Risk factors for overall mortality beyond the first postoperative year include male gender, age, pre- and posttransplant diabetes, posttransplant hypertension, posttransplant renal insufficiency, retransplantation, pretransplant malignancy, and metabolic liver disease. Optimal management of cardiovascular disease, diabetes, hypertension, malignancy and renal insufficiency are thus all necessary to reduce long-term mortality for liver transplant recipients. Although considerable attention has been given to center specific variability in one year posttransplant survival, there is much greater center to center variation in longterm outcomes, e.g. 3 yrs posttransplant (Figure 3, data source SRTR. http://www.srtr.org/). The great majority of variation in longterm outcomes between centers cannot be accounted for recipient or donor-specific parameters.

The Rise of Posttransplant Metabolic Syndrome

Metabolic syndrome (MS), as defined by the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), is a constellation of physiological consequences of obesity, including increased abdominal girth, hypertension, hyperglycemia and dyslipidemia. The metabolic syndrome is an important factor for nearly all of the major causes of longterm posttransplant mortality, including cardiovascular disease, renal insufficiency and neoplasia. Enhancing posttransplant outcomes requires minimizing the impact of posttransplant MS.

The prevalence of MS varies with the etiology of liver disease. Patients with cryptogenic cirrhosis, for example, have a higher reported prevalence of MS (29%) than patients with other etiologies of liver disease (~6%).(3) The lower pre transplant prevalence of MS almost certainly relates, at least in part, to the low systemic vascular resistance with associated systemic hypotension that is a hallmark of portal hypertension combined with the low lipid levels (with the exception of primary biliary cirrhosis) associated with chronic liver disease and cirrhosis, reducing the frequency of criteria for metabolic syndrome in patients with cirrhosis. As portal hypertension resolves, the prevalence of features of MS increases following liver transplantation, with the absolute prevalence of diabetes rising from ~15% to over 30% after transplantation, hypertension rising from ~15% to over 60% after transplantation and hyperlipidemia occurring in over 50% of liver transplant recipients.(4) Overall, MS is present in ~50% of patients after transplantation and is associated with increased cardiovascular and cerebrovascular events.(4)

Components of Metabolic Syndrome Post-Liver Transplant

Obesity

Obesity is the physiological engine of MS. The globally increasing average BMI has been mirrored by the BMI of patients undergoing liver transplantation. Over a third patients with end-stage liver disease are obese.(5, 6) Between 1990 and 2012, the proportion of liver transplant recipients classified as obese increased from 15% in the early 1990’s to just over 25% since 2002, and 27% in 2012, with an increase in average recipient weight of approximately 1 kg per year.(7) With few exceptions, patients that are overweight or obese prior to transplant will remain overweight or obese after, with ~one third of patients of normal weight at the time of transplant becoming obese posttransplant.(7) The potential impact of posttransplant weight gain includes increased risk of diabetes and metabolic syndrome and associated complications, including cardiovascular disease, renal disease and non-alcoholic steatohepatitis in the allograft. As
in the non-transplant setting, sustained weight reduction is difficult to achieve posttransplant. The comparative effectiveness of a multidisciplinary protocol for obese patients requiring liver transplantation, including a noninvasive pretransplant weight loss program, with and without a combined liver transplant plus sleeve gastrectomy for obese patients who failed to lose weight prior to liver transplantation has recently been described. In 37 patients who received liver transplantation alone, weight gain to BMI >35, posttransplant diabetes (DM), hepatic, deaths and grafts loss were all less frequent among the 7 patients undergoing the combined liver transplant/sleeve gastrectomy procedure. While the role of bariatric surgery continues to evolve during and after liver transplantation, these preliminary results suggest that combined liver transplantation plus sleeve gastrectomy might be considered in appropriate patients with persistent pretransplant obesity and metabolic syndrome.

Posttransplant Pharmacotherapy of Obesity

The impact of the two newly approved therapies for obesity, lorcaserin (a selective 5-HT2C agonist) and phentermine/topiramate extended-release, have not been reported. Because lorcaserin (Belviq) is metabolized by multiple pathways and multiple enzymes, immunosuppressive agents, are predicted to have minimal impact on lorcaserin exposure and vice versa. In addition lorcaserin does not require dose adjusting in mild to moderate renal insufficiency or hepatic impairment, both of which are common following liver transplantation. Lorcaserin would appear to have a superior safety profile to phentermine/topiramate. Ezetimide, an agent that inhibits the enterohepatic recirculation of lipids and has minimal cytochrome P450 metabolism, has been shown to be well tolerated and effective when used in combination with statin drugs in a small retrospective study of liver transplant patients. There is a theoretical concern of hepatotoxicity for ezetimide, particularly when used with statins, thus caution should be exercised until more data is available in liver transplant recipients. Tetrahydrolipstatin (Orlistat), a reversible inhibitor of pancreatic lipase, has been investigated in the posttransplant setting and appears to be of limited efficacy and may interfere with immunosuppression absorption. Bariatric surgery prior to transplant is a difficult proposition in patients with portal hypertension, but may be an option in carefully selected patients.

Diabetes

Glucose intolerance is common in cirrhosis, largely due to peripheral insulin resistance. While a small minority of patients will experience improved insulin sensitivity after liver transplant, more will either remain diabetic or develop new onset diabetes (NOD) after liver transplant, with about a third of liver transplant recipients developing long-term diabetes after transplantation. The majority of NOD (80%) develops within 1 month of transplant. Diabetes significantly affects posttransplant outcomes, particularly in patients transplanted with hepatitis C. The 5-year occurrence of advanced fibrosis is increased in patients treated for diabetes mellitus (49%) when compared to patients with normal insulin sensitivity (20%). Posttransplant DM is also significantly associated with late onset hepatic artery thrombosis, acute and chronic rejection. Overall patient morbidity and mortality are greater in patients with both pre- and posttransplant diabetes, even when posttransplant diabetes is transient.

Pre-transplant diabetes, elevated BMI, hepatitis C infection (HR 2.5, P=0.001) and methylprednisolone boluses (HR 1.09 per bolus, P=0.02) are independent risk factors for the development of NOD. The transplanted liver itself may contribute to the increase in insulin resistance as denervation/vagotomy of the liver during liver transplantation has been associated with increased insulin resistance. Posttransplant immunosuppression typically impairs insulin sensitivity. Corticosteroids, for example, induce insulin resistance in a dose-dependent manner by decreased beta-cell insulin production, increased gluconeogenesis and decreased peripheral glucose utilization. Calcineurin inhibitors (cyclosporine and tacrolimus) both decrease insulin synthesis and secretion (pancreatic beta-cell toxicity) and induce insulin resistance and hyperinsulinemia. Sirolimus, an mTOR inhibitor, blocks B-cell proliferation, theoretically increasing the risk for diabetes, but also increases GLUT-4 signalling in insulin responsive cells. The net effect of the mTOR inhibitors everolimus and sirolimus on posttransplant diabetes is not known.

In the nontransplant population, target glycosylated hemoglobin is <7%, fasting blood sugar 70-130 mg/dL (3.9-7.2mmol/L), and peak post prandial glucose <180mg/dL (10mmol/L). Treatment of early posttransplant diabetes is largely with insulin. As steroids are tapered, lifestyle modifications (diet and physical exercise) should be encouraged and conversion to an oral hypoglycemic agent considered. Most oral hypoglycemic agents have not been formally studied in the posttransplant setting. In the
Nontransplant setting, weight gain and hypoglycemia are less common with biguanides (metformin) than sulfonylureas or thiazolidinediones. Metformin should be avoided in the setting of renal failure, which is common among liver transplant recipients, due to the increased risk of lactic acidosis. Annual retinal exams, urinary protein screening and foot care should be encouraged for liver transplant recipients with diabetes.

**Dyslipidemia**

Dyslipidemia affects ~two thirds of liver transplant recipients(18) and is a major risk factor for posttransplant cardiovascular-related morbidity and mortality.(19) Although tacrolimus may be associated with less severe and lower frequencies of dyslipidemia than cyclosporine, both agents are associated with hyperlipidemia.(20) Sirolimus and everolimus are potent hyperlipidemic agents,(21, 22) possibly by affecting the insulin signaling pathway, increasing adipose tissue lipase activity, and decreasing lipoprotein lipase activity. The basis of the relatively dyslipidemic effects of cyclosporine are not known but may involve inhibition of hepatic bile acid 26-hydroxylase, decreasing bile acid synthesis from cholesterol and reducing the subsequent transport of cholesterol into bile and the intestine. Cyclosporine binds to the low-density lipoprotein (LDL)-cholesterol receptor, increasing circulating levels of LDL-cholesterol. Tacrolimus appears less likely to cause hypercholesterolemia than cyclosporine, with conversion of recipients to tacrolimus from cyclosporine in the setting of persistent hypercholesterolemia showing some evidence of efficacy in the management of posttransplant dyslipidemia.(23) Posttransplant dyslipidemia is generally resistant to dietary interventions. Calcineurin inhibitor dosing should probably be minimized in patients with posttransplant MS and dyslipidemia. Corticosteroids are known to produce insulin resistance, truncal fat deposition, hypertension and dyslipidemia. Only a small minority of patients require maintenance corticosteroids, which can typically be discontinued before the end of the first postoperative year. Pharmacotherapy should be considered in patients with persistent hyperlipidemia. HMG CoA inhibitors (statins), which are well tolerated in solid organ recipients,(24) are an appropriate first line agent for recipients with both elevations in cholesterol and triglycerides. Statins have been used commonly in solid organ transplant recipients for decades and are well tolerated. Pravastatin is the most studied in transplant recipients and has the theoretical advantage metabolism that its metabolism does not require the P450 enzyme system. Other statins (atorvastatin, simvastatin, lovastatin, cerivastatin and fluvastatin) are also used frequently in transplant patients. A small reduction in cyclosporine and tacrolimus levels during statin therapy has been reported. Simvastatin (40mg/day), atorvastatin (40mg/day) or pravastatin (20mg/day) are reasonable starting doses for posttransplant hypercholesterolemia, in combination with a controlled diet, e.g. a Mediterranean diet rich in omega-3 fatty acids, fruits, vegetables and dietary fiber.

Isolated hypertriglyceridemia is also common following liver transplantation and may respond to fish oil (omega 3) which has an excellent safety profile and minimal drug interactions.(25) A starting dose of 1,000mg BID, increasing to a total of 4,000mg daily in divided dosing is reasonable. Fish oil does not affect cyclosporine (a highly lipophilic agent) or tacrolimus levels significantly.(26) Doses above 4,000mg can have antiplatelet effects and increase risk of bleeding. Some patients may experience an increase in LDL levels on fish oil. Alternative agents for patients with hypertriglyceridemia include the fibric acid derivatives (gemfibrozil, clofibrate, fenofibrate), which are generally well tolerated but have occasionally been associated with myositis, particularly if used with statins. Fibrates are highly protein bound and cytochrome P450 metabolized with some evidence of a mild effect of increasing calcineurin inhibitor levels.(26)

Ezetimide, an agent that inhibits the enterohepatic recirculation of lipids and has minimal cytochrome P450 metabolism, has been shown to be well tolerated and effective when used in combination with statin drugs in a small retrospective study of liver transplant patients.(9) There is a theoretical concern of hepatotoxicity for ezetimide, particularly when used with statins, thus caution should be exercised until more data is available in liver transplant recipients.

**Hypertension**

Hypertension is unusual prior to transplantation but occurs in ~70% of liver transplant recipients.(4) Steroids contribute to posttransplant hypertension through mineralocorticoid effects and by increasing SVR and cardiac contractility. Sirolimus increases the risk of hypertension when added to calcineurin inhibitors.(27) Calcineurin inhibitors are a major cause of posttransplant hypertension, largely related to renal (and systemic) vasoconstriction, as well as impaired GFR and sodium excretion. Because of the contribution of renal arteriolar vasoconstriction to posttransplant hypertension, calcium channel blockers (amlodipine, isradipine and felodipine) are excellent first line agents. Nifedipine is an inhibitor of intestinal cytochrome P450, predictably increasing CNI.
levels with potential for CNI toxicity, and may cause leg edema. Second line therapies include specific beta blockers (non-specific beta blockers may reduce portal blood flow), ACE inhibitors, angiotensin receptor blockers and loop diuretics. ACE inhibitors and angiotensin receptor blockers may exacerbate CNI-induced hyperkalemia, but may also protect against calcineurin-induced renal injury (28). Thiazides and other diuretics should be used with caution in transplant recipients due to potentiation of electrolyte abnormalities and a mechanism of action that is relatively removed from the physiology of posttransplant hypertension. Up to 30% of liver transplant recipients require two or more antihypertensives to achieve blood pressure goals.

**Cardiovascular Disease**

Cardiovascular disease is a leading cause of morbidity and mortality in liver transplant patients. About a quarter of liver transplant recipients have underlying coronary artery disease.(29) The 10 year probability of a coronary event is higher in liver transplant recipients (11%) than the general population (7%).(30) The relative risk of ischemic cardiac events is ~ three fold greater in liver transplant recipients when compared to age and sex match general population.(31) Minimization of cardiovascular events following liver transplantation revolves around effective pretransplant screening, e.g. with stress echocardiography and serum troponin levels(19) and management of the components of the metabolic syndrome.

**Malignancy**

The probability of liver transplant recipients developing de novo malignancy at 1, 5, and 10 years

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Breast</td>
<td>Women 50 to 74: annual screening; other ages: screening left to the patient and physician.</td>
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<tr>
<td>Skin</td>
<td>Monthly self examination; physician examination annually.</td>
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<tr>
<td>Cervical</td>
<td>All women 21 to 65 years old with I Pap smear and pelvic examination every 3 years.</td>
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<tr>
<td>Anogenital</td>
<td>Yearly physical examination of the anogenital area, including pelvic examination and cytologic studies for women.</td>
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<tr>
<td>Prostate</td>
<td>Consider annual screening for men ≥ age 50. If positive family history or African American race, may start annual screening earlier.</td>
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<tr>
<td>Colorectal</td>
<td>Starting at age 50: annual FOBT and colonoscopy every 10 years (or FOBT every 3 years with flexible sigmoidoscopy every 5 years).</td>
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<tr>
<td>Lung</td>
<td>Annual CXR if history of smoking.</td>
</tr>
<tr>
<td>HCC</td>
<td>For patients with cirrhosis of active HCV or HBV infection, serum AFP and liver ultrasound every 6 to 12 months.</td>
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posttransplantation is 4%, 12%, and 22%, respectively.\(^{32}\) This is about twice the risk for matched non-transplant patients. About half of posttransplant malignancies are skin cancers. The probability of developing nonskin malignancy is significantly higher in patients with primary sclerosing cholangitis (PSC; 22% at 10 years) or alcohol-related liver disease (ETOH; 18% at 10 years); when compared to all other diagnoses (10% probability)(Figure 4). In multivariate analyses increased age by decade (hazard ratio [HR] = 1.33, \(P = .01\)), a history of smoking (HR = 1.6, \(P = .046\)), are associated with increased risk for development of solid malignancies after liver transplantation. The development of hematologic and solid organ malignancies greatly affects survival, with probabilities of death after diagnosis of \(\sim 40\%\) at 1 year. The increased risk for malignancies among liver transplant recipients is multifactorial, with important attributable risks including exposure to chronic immunosuppression, concomitant viral infection (e.g. Ebstein-Barr), and sun exposure. Much of the increased risk for skin and non-skin malignancies in liver transplant recipients is on the basis of immunosuppression, with good evidence that reducing immunosuppression reduces risk of malignancy.\(^{33}\) A summary of recommendations for cancer screening in solid organ recipients adapted to liver transplantation is provided in Table 1.\(^{34}\)

Because of the clear role of immunosuppression in posttransplant malignancy risk and MS, consideration should be given to finding the minimal amount of immunosuppression required to maintain excellent graft function.

**References**


